# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-929**

# PHARMACOLOGY REVIEW(S)

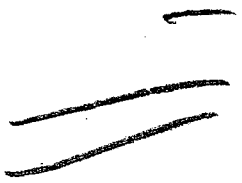
Trout

SEP 2 1 1999

# REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

**KEY WORDS:** Impurity qualification
**Reviewer Name:** W. Mark Vogel, Ph.D.
**Division Name:** Division of Pulmonary and Allergy Drug Products
**HFD#:** HFD-570
**Review Completion Date:** September 21, 1999
**Review Number:** Review #3
**Application Number:** NDA 20-929
**Serial Number:** None
**Submission Date:** March 24, 1999
**Submission Type:** General correspondence
**Information to Sponsor:** Yes ( ), No (✓)
**Applicant:** Astra Pharmaceuticals

**Drug:**
*Code Name:* S-1320 (RS) S-1322 (R) S-1321 (S)
*Generic Name:* Budesonide nebulizing suspension
*Trade Name:* Pulmicort Respules™
*Chemical Name:* (RS)11β,16α17,21,tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde
*CAS Registry Number:* 51333-22-3
*Molecular Formula:* $C_{25}H_{34}O_6$
*Molecular Weight:* 430.5
*Structure:*



**Relevant INDs/NDAs:**
IND 21,632 & NDA 20-233 Astra, Rhinocort (budesonide) Nasal Inhaler
IND 31,308 & NDA 20-441 Astra, Pulmicort (budesonide) Turbuhaler
IND 44,535 Astra, Budesonide Nebulizer solution
NDA 20-746, Astra, Rhinocort Aqua

**Previous Reviews:**

| Submission | Date | Reviewer | Date |
|---|---|---|---|
| Original NDA | 18 NOV 97 | Mark Vogel | 28 APR 98 |
| Response to approvable letter | 07 AUG 98 | Mark Vogel | 04 DEC 98 |

**Drug Class:** Glucocorticoid steroid
**Indication:** Asthma
**Route of Administration:** Oral Inhalation
**Proposed Clinical Use:**

**Studies Reviewed within this Submission:** No formal study reports were included with this submission. The submission is a rationale for proposed drug impurity specifications.

**Studies Not Reviewed within this Submission:** N/A
**Studies Previously Reviewed:** N/A

*Note: Portions of this review were excerpted directly from the sponsor's submission.*

**Introduction/Drug History:** The NDA for this product is currently under review. An approvable letter was sent by the Division dated 20 May 1998. A response to the approvable letter was submitted 07 August 1998. The application is still awaiting further response from the applicant primarily to address chemistry issues. Budesonide is approved for nasal inhalation in allergic rhinitis (Rhinocort, NDA 20-233, approved 14 FEB 97) and as a dry powder inhaler for asthma (Pulmicort Turbuhaler, NDA 20-441, approved 24 JUN 97). The present submission is a rationale for proposed drug substance and drug product specifications for the drug-related impurity ——— This is an impurity that is quantified by new analytical methods. This impurity had been identified previously during the development of budesonide-containing products but is not being routinely quantified by current analytical methods. This impurity is also contained in other approved or pending budesonide NDAs and the submission is cross-referenced to these NDAs: NDA 20-441, Pulmicort Turbuhaler; NDA 20-233, Rhinocort Nasal Inhaler; NDA 20-746, Rhinocort Aqua Nasal Spray.

## OVERALL SUMMARY AND EVALUATION

Astra proposes specifications (for products under review) or action limits (for approved products) for ——— in budesonide drug substance and various budesonide drug products as summarized in Table 1 on the following page. All ——— levels are expressed as a % of parent budesonide. The proposed specification for ——— in budesonide drug substance, not more than (NMT) ——— exceeds the ICH qualification threshold for drug-related impurities in drug substance (0.1%). The proposed specifications for 11-ketobudesonide are below the ICH qualification threshold for drug product degradation impurities (1% for daily intake ≤ 10 mg) [redacted]

[redacted] ; the specification for total degradation products is NMT ——— There are two strengths of Rhinocort Aqua (32 µg and 64 µg per spray). The proposed specification for ——— in drug product is NMT ——— for both strengths.

**Table 1. Proposed Specifications and Maximum Exposures to**

| | Drug Substance | Pulmicort Turbuhaler | Rhinocort Inhaler | Pulmicort Respules | Rhinocort Aqua |
|---|---|---|---|---|---|
| NDA number | | 20-441 | 20-233 | 20-929 | 20-746 |
| Specification (NMT) | | | | | |
| Highest observed level | | | | | |
| **Adults** | | | | | |
| Maximum Budesonide dose (µg) | 1600† | 1600 | 256 | | 256 |
| Assumed Body Weight (kg) | 50 | 50 | 50 | | 50 |
| Max. Budesonide dose (µg/kg) | 32† | 32 | 5.12 | | 5.12 |
| Max. Budesonide dose (µg/m²) | 1184† | 1184 | 189 | | 189 |
| Max. dose (µg/m²) | | | | | |
| Based on specified maximum | | | | | |
| Based on observed maximum | | | | | |
| **Children** | | | | | |
| Maximum Budesonide dose (µg) | 1000† | 800 | 256 | 1000 | |
| Minimum indicated age (yr) | 1 | 6 | 6 | 1 | 6 |
| Assumed Body Weight (kg) | 10 | 20 | 20 | 10 | 20 |
| Max. Budesonide dose (µg/kg) | 100† | 40 | 12.8 | 100 | |
| Max. Budesonide dose (µg/m²) | 2500 | 1000 | 320 | 2500 | |
| Max. dose (µg/m²) | | | | | |
| Based on specified maximum | | | | | |
| Based on observed maximum | | | | | |

Highlighted values indicate impurity specifications above the applicable ICH qualification thresholds. * Specification is for total related impurities not in particular. † Maximum dose of drug substance is based on product with highest dose (Turbuhaler for adults, Respules for children). ‡ This updated specification is from a Chemistry submission dated 30 AUG 99, see chemistry review dated 08 SEP 99.

To qualify the proposed specifications the applicant submitted assay data on drug lots previously used in animal toxicity studies. The values for were determined from previous original HPLC chromatograms from those lots. The original analytical method did not specifically measure but a peak is observed in those chromatograms that was later shown to correspond to The applicant submitted data for batches used in 15 general toxicity studies and two genotoxicity studies. Data from three studies of at least 3-months duration with the highest calculated doses of are summarized in Table 2 on the following page. The highest administered dose of in inhalation studies was (6-month dog). This is not a NOAEL dose but the highest dose administered in the toxicity study. However, all of the observed adverse effects were typical glucocorticoid effects. Thus, up to an inhalation dose of there were no unexpected adverse effects observed that might be attributed to this impurity. This value is ~2.2 times the maximal theoretical dose of from the drug substance in adults (based on Pulmicort Turbuhaler), and

is about equal to the maximal theoretical dose of [redacted] from the drug substance in children (based on Pulmicort Respules). The maximum inhalation dose of [redacted] in the 6-month dog inhalation study is ~1.4 times the dose of [redacted] in adults or ~0.8 times the dose of [redacted] in children for total degradants including [redacted] in Rhinocort Nasal Inhaler. However, the dose ratios are much greater when the human [redacted] doses are calculated based on the highest observed levels of [redacted] in Rhinocort Nasal Inhaler. Then, the dose of [redacted] of [redacted] in the dog study is ~18-times the human adult dose and ~12-times the children's dose. The oral rat study provides about 1.8-fold greater dose ratios for potential systemic activity of [redacted] but does not address potential airway effects.

**Table 2. Levels of [redacted] in Animal Toxicity Studies**

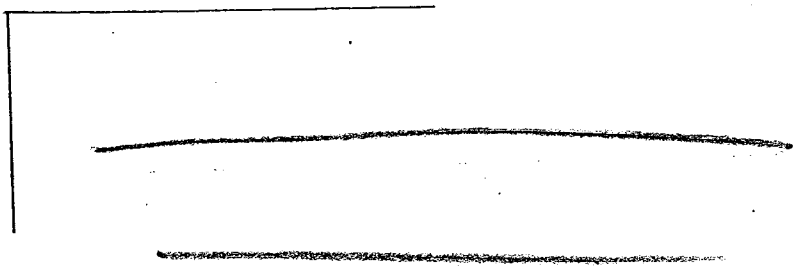
| Species | Dog | Rat | Rat |
|---|---|---|---|
| Route | inhalation | inhalation | Oral |
| Duration | 6-month | 3-month | 3-month |
| Study # | 76079 | 78/ADA2/156 | 610-146 |
| Batch # | 2/76 | 2/76 | 64/79 |
| Assay 1 date | 27-Aug-76 | 27-Aug-76 | 19-Feb-79 |
| Assay 1 (%) | [redacted] | | |
| Assay 2 date | 21-Dec-76 | 21-Dec-76 | 11-Nov-81 |
| Assay 2 (%) | [redacted] | | |
| Study start | Sept. 1976 | May 1976 | March 1980 |
| Estimated % at study start* | [redacted] | | |
| Estimated % at study end* | [redacted] | | |
| Avg. % during study | [redacted] | | |
| Budesonide high dose (µg/kg) | 200 | 428 | 700 |
| Budesonide high dose (µg/m²) | 4000 | 2568 | 4200 |
| [redacted] high dose (µg/m²) | [redacted] | | |

* Assumes a linear increase in [redacted] and a minimum initial concentration of [redacted] (lowest observed in recent batches).

In addition to the exposure data from animal toxicity studies, further data were presented to justify the proposed levels of [redacted] First, it is well known from structure activity relationships that an [redacted]. The applicant reports that the topical anti-inflammatory activity of [redacted] was tested in an ear-edema assay in rats and mice. The local potency relative to budesonide was [redacted] in mice and rats, respectively. The systemic potency of [redacted] to induce involution of thymus and reduce body weight in rats was [redacted] relative to budesonide (original data on file at Astra Draco).

Secondly, other steroids with an ——— have been used clinically for many years. These include ——— whose structures are shown in Figure 1 on the following page. These steroids lack intrinsic ——— activity. Instead they are converted, in the body, to the active ——— ——— by the enzyme ——— This enzyme can work in both directions, converting ——— steroids to ——— and vice versa. The ——— is a substrate for this enzyme. ———

In vitro studies with liver microsomes from mice, rats, and humans do not show conversion of budesonide to ———



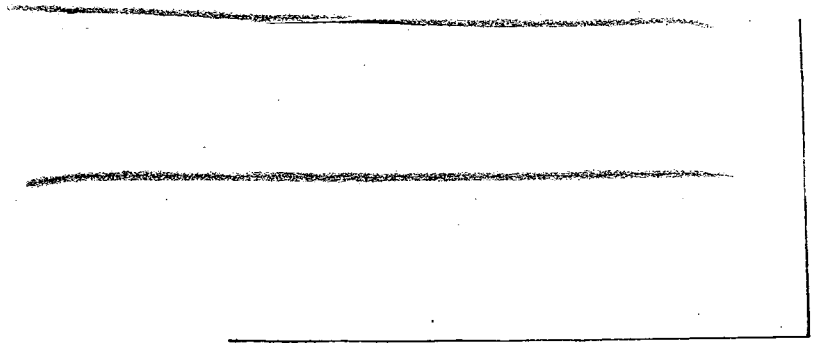


**Figure 1.** Structures of some ——— Arrow indicates ———

In summary, ——— is a drug-related impurity in budesonide drug substance and a degradant in several budesonide drug products. Under the ICH guidance,

toxicological qualification is required to support the proposed specifications of [redacted] in drug substance and [redacted] total related impurities [redacted] The proposed specifications for [redacted] as a degradant in the other budesonide drug products is below the qualification threshold of 1%. Pharmacology studies have shown that [redacted] has only weak glucocorticoid potency in vivo, as expected from known structure-activity relationships. No toxicity other than expected glucocorticoid effects was observed in rat and dog inhalation studies ≥ 3-months duration with maximum calculated exposures to [redacted] of [redacted] in the 6-month dog study. This is ~2.2-times the maximum dose of [redacted] from drug substance in adults and about equal that for children. For Rhinocort Nasal Inhaler, the dose of [redacted] in the dog study is ~1.4 times the dose in adults and ~0.8 times the dose in children for total permitted degradants. However, the inhalation dose of [redacted] in dogs was ~18-times the human adult dose and ~12-times the children's dose based on the highest observed levels of [redacted] in Rhinocort Nasal Inhaler. Maximum oral dose of [redacted] in rats was about 2-fold greater on a µg/m² basis. [redacted] does not appear to be a metabolite of budesonide in humans or animals. However, the corresponding [redacted] There is also considerable clinical experience with [redacted] which are considered to be inactive until converted to the [redacted] The [redacted] is not a structural alert for genotoxic activity.

APPEARS THIS WAY
ON ORIGINAL

## RECOMMENDATIONS

1. The proposed specification of [redacted] in budesonide drug substance is supported by a combination of inhalation and oral toxicity studies in rats and dogs, plus experience with related [redacted] steroids and steroid metabolites.
2. Based on ICH guidance (1% threshold), no toxicological qualification is required for the proposed drug product specifications of [redacted] (or total impurities) in: Rhinocort Aqua (NMT [redacted] Pulmicort Turbuhaler (NMT [redacted] total related impurities), or Pulmicort Respules (NMT [redacted] total impurities and degradation products).
3. The maximum observed level of [redacted] in Rhinocort Nasal Inhaler [redacted] does not present a safety concern. However, the specifications for this product should be redrawn to set limits for particular impurities (including [redacted] that reflect the maximum observed levels.

/S/ 3/21/99

Mark Vogel, Ph.D., Pharmacologist

Original NDA 20-929
c.c. Original NDA 20-233
Original NDA 20-441
Original NDA 20-746
HFD-570/Division File NDA 20-929
HFD-570/Division File NDA 20-233
HFD-570/Division File NDA 20-441
HFD-570/Division File NDA 20-746
HFD-570/C.J. Sun
HFD-570/R. Huff
HFD-570/L. Sancilio
HFD-570/L. Pei
HFD-570/T. McGovern
HFD-570/G. Trout
HFD-570/E. Nashed
HFD-570/D. Kobel
HFD-570/C-H. Kim
HFD-570/G. Poochikian
HFD-570/W.M. Vogel

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# DIVISION OF PULMONARY DRUG PRODUCTS
# REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

## Chemistry Consult, Original Review No. 5

| | |
|---|---|
| **NDA No.** | 20-746, 20-233, 20-441, 20-929 |
| **Content of Consult Request:** | Safety evaluation of an budesonide impurity – |
| **Date and Reviewer Requesting the Consult:** | April 21, 1999 in NDA 20-929<br>Dr. Eugenia Nashed (Chemist) |
| **Pharmacology/Toxicology Reviewer:** | Luqi Pei, D.V.M., Ph.D. (HFD-570) |
| **Date of Review Completed** | May 18, 1999 |
| **Sponsor:** | Astra USA, Westborough, MA. |
| **Drug Name:** | Rhinocort AQ Nasal Spray (Budesonide) |

This review evaluates the safety of [redacted] an impurity present in 2 budesonide products under development by Astra. I find that the sponsor has not established the safety of this impurity in their products because I have concerns about genetic toxicity of [redacted] has an [redacted] hat bears structural alert for genotoxicity. Additional testing (e.g., genetic toxicity testing) is needed to qualify [redacted] The review is written in these four sections: issue, background, evaluation, and recommendation.

**Issue:**

Astra drug products contain an impurity, [redacted] at concentrations within the ICH threshold limits (1.0%) for qualifying impurities in drug products; however, [redacted] bears structural alert. ICH guidelines states that its qualification threshold can be modified, "based on scientific rationale and level of concern". This situation raises an issue whether Astra needs additional testing to qualify their new products.

**Background:**

Although present in all Astra budesonide products, [redacted] was not an issue in the previous NDAs (Pulmicort and Rhinocort) because these products contain its relatively low concentrations of [redacted] The specifications for Pulmicort was set at [redacted] its specification in Rhinocort is not clear. [redacted] becomes an issue with the new formulations (Pulmicort Respule and Rhinocort Aqua) only because Astra proposes higher [redacted] specifications. The proposed specifications are not-more-than [redacted] and approximately [redacted] for Pulmicort Respule and Rhinocort Aqua, respectively.

The Rhinocort Aqua review team has been addressing the [redacted] issue since the beginning of the application. Astra originally proposed specifications of [redacted] for their 64 µg strength and 32 µg strength. Drs. Hilary Sheevers and Luqi Pei conducted the safety evaluation of [redacted] under the request of Dr. Linda Ng (previous Chemist Reviewer) on October 22, 1996. The Pharm/Tox review team recommended that the Astra comply with the ICH guidelines for impurities and keep [redacted] levels [redacted] (See Dr. L. Pei's review dated May 30, 1997.) The ICH threshold of qualification for impurities in final drug products is 1.0% for drugs with a total daily dose of 10 mg/kg or less. The total daily dose of budesonide in Astra products is [redacted] or less. No preclinical testing is routinely necessary for impurity concentration below the qualification threshold.

The Division asked Astra to tighten their specification for [redacted] "to reflect the data" (Division's Approvable Letter of October 29, 1997).

A few other changes have occurred in the Division since then. The Astra application is now in the second review cycle. Dr. Eugenia Nashed replaced Dr. Linda Ng as the chemistry reviewer. A new procedure regarding review process for impurities and extractables between chemistry and pharmacology has been set recently. Chemist reviewers are to inform the Pharma/Tox reviewer structural alert of any impurities and extractables. On April 21, 1999, Dr. Nashed found [redacted] bearing structural alert and requested a re-evaluation of [redacted] safety.

The structural alert prompted the Division take additional action recently. In the letter of May 6, 1999 to Astra, the Division wrote:

> "We are concerned with relatively high levels (up to [redacted], of this deposition compound in the drug product, since it constitutes structural concern for genotoxicity and airway irritation. Provide a short summary of any corrective actions implanted to slow down the oxidation process. Also, submit data on the levels of this degradation product present in the preclinical batches or any other data for toxicological qualification of the impurities."

**Evaluation:**

Astra has four budesonide drug products regulated by this Division that are either on the market or under development. Table 1 lists the proposed or expected levels and the corresponding daily doses of [redacted] in these Astra budesonide products. The [redacted] concentrations in Astra drug products are [redacted] or less. This correspond to an expected human daily dose of [redacted] is [redacted] ng/kg/day or less.

Table 1. [redacted] Levels in Astra's Drug Products

| | | Reviewer | | Specification | | Max Dose* (μg/kg) | |
|---|---|---|---|---|---|---|---|
| NDA # | Product | Chemist | Pharm/T | Substance | Product | Budes. | [redacted] |
| 20-233 | Rhinocort | Koble | Sancilio | | | | |
| 20-441 | Pulmicort | Koble | Sancilio | < [redacted] | | 32 | [redacted] |
| 20-746 | Rhinocort Aqua | Nashed | Pei | | [redacted] | 5.1 | [redacted] |
| 20-929 | Pulmicort Respule | Kim | Vogel | < [redacted] | NMT [redacted] | 20 | [redacted] |

The ICH threshold limit of qualification for impurities in drug products with a total daily dose of less than 10 mg is 1.0%. The ICH guidelines also indicate that this limit can be modified; " Higher or lower threshold for qualification of degradation products may be appropriate for some individual drug products based on scientific rationale and level of concern...." [redacted] bears structural alert and increases the level of concern. Therefore, its threshold should be lowered and qualification is needed for the proposed concentration of [redacted]

The major safety concern of [redacted] is its potential genetic toxicity raised by the structural alert and its carcinogenicity associated with the genotoxicity. Airway irritation is a minor concern because its relatively low dose and potential mild irritability. Also, irritability may have been easily assessed in clinical and preclinical studies if batches of testing formulations contain the sufficient level of the degradation product. [redacted] at the proposed level is unlikely to produce significant systemic toxicity.

The ICH guidelines have set criteria for impurity qualification. These include: 1) to-be-marketed formulation with the impurity in question being testing in preclinical or clinical trials, 2) lowing the impurity levels, 3) literature data, or 4) additional preclinical testing. Criteria 4 is considered only if the first three criteria fail. The ICH guidelines further define additional preclinical testing as *in vitro* genetic toxicity testing and general toxicity studies with the testing duration of between 14 to 90 days.

The Divison has asked Astra to review [redacted] levels in preclinical and clinical testing batches. Currently, it is unclear whether batches in previous clinical trials contain the impurity at sufficiently high levels. Even if [redacted] is present at a level of approximately [redacted] in animal toxicity studies and clinical trial, they are not sufficient to override the concern on genotoxicity because short term studies are not designed to test genotoxicity and carcinogenicity of a testing compound. Therefore, the lack of information on genotoxicity and carcinogenicity of [redacted] warrants screen testing for its genotoxicity potential. Additional evaluation of [redacted] may be needed if the genetic toxicity testing yields positive results.

**Recommendation:**

1). Keep the level of [redacted] or less. Or

2). Conduct two *in vitro* genetic testing of the impurity: one for point mutation (e.g. bacterial

mutation test) and the other chromosomal aberration (e.g. mouse lymphoma assay).

3). Additional evaluation of —— may be needed when the genetic testing yields positive results.

/S/ 5/18/99

Luqi Pei, D.V.M., Ph.D.
Pharmacologist/Toxicologist

/S/ 5.18.99

W. Mark Vogel , Ph.D.
Acting Team Leader

cc: HFD-570/Pei/[redacted]/Nashed/Trout

DEC - 4 1998

# REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Review #2

| | |
|---|---|
| **KEY WORDS:** | Labeling, inhalation toxicology, juvenile animals. |
| **Reviewer Name:** | W. Mark Vogel, Ph.D. |
| **Division Name:** | Division of Pulmonary Drug Products |
| **HFD#:** | HFD-570 |
| **Review Completion Date:** | December 04, 1998 |
| **Electronic File Number:** | not applicable, entered into DFS |
| **NDA Number:** | 20-929 |
| **Serial Number:** | N 000/AZ |
| **Submission Date:** | August 07, 1998 |
| **Submission Type:** | Complete response to Division's approvable letter dated May 20, 1998 |
| **Information to Sponsor:** | Yes (✓), No ( ) |
| **Sponsor or Agent:** | Astra Pharmaceuticals, Westborough, MA |

| | | |
|---|---|---|
| **Drug:** | *Code Name:* | S-1320 (RS) S-1322 (R) S-1321 (S) |
| | *Generic Name:* | Budesonide nebulizing suspension |
| | *Trade Name:* | Pulmicort Respules™ |
| | *Chemical Name:* | (RS)11β,16α17,21,tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde |
| | *CAS Registry Number:* | 51333-22-3 |
| | *Molecular Formula:* | $C_{25}H_{34}O_6$ |
| | *Molecular Weight:* | 430.5 |
| | *Structure:* | |

[redacted]

**Relevant INDs/NDAs:**

IND 21,632 & NDA 20-233 Astra, Rhinocort (budesonide) Nasal Inhaler
IND 31,308 & NDA 20-441 Astra, Pulmicort (budesonide) Turbuhaler
IND 44,535 Astra, Budesonide Nebulizer solution

**Previous Reviews:**

Original NDA 20-929, Reviewed by W. Mark Vogel, Ph.D., April 28, 1998
NDA 20-233 Reviewed by Conrad H. Chen, Ph.D., July 23, 1993
NDA 20-441 Reviewed by Lawrence F. Sancilio, Ph.D., Luqi Pei, Ph.D., June 11, 1996
Report of the Carcinogenicity Assessment Committee, September 03, 1993
IND 44,535, serial N132, submitted 21 APR 1996, Reviewed by S. Tripathi, September 30, 1997

**Drug Class:**. Glucocorticoid steroid
**Indication:** Asthma

**Clinical Formulation (and components):** Drug is formulated as a sterile suspension of budesonide in aqueous vehicle for delivery by nebulizer. Unit doses are packaged in individual ampules in different strengths; each ampule contains 2 mL of suspension.

| | | 0. 5 mg/2mL | 1.0 mg/2mL |
|---|---|---|---|
| | | mg/mL | mg/mL |
| Budesonide (micronized) | | 0.25 | 0.5 |
| Edetate disodium ( , USP | | | |
| Sodium chloride, USP | | | |
| Polysorbate 80, NF | | | |
| Citric acid ( , USP | | | |
| Sodium citrate, USP | | | |
| Water for injection, USP | | | |

**Route of Administration:** Oral Inhalation

**Studies Reviewed within this Submission:**

1. General Toxicity of budesonide nebulizing suspension administered by the inhalation route to 2-week old beagle pups for a period of 3 months. Astra Study Code 850-TO-0151, Report number SR97214-01, May 08, 1998.
2. Revised labeling.

**Studies Not Reviewed within this Submission:** None

*Note: Portions of this review were excerpted directly from the sponsor's submission.*

**Introduction/Drug History:** Budesonide is approved for nasal inhalation in allergic rhinitis (Rhinocort, NDA 20-233, approved 14 FEB 97) and as a dry powder inhaler for asthma (Pulmicort Turbuhaler, NDA 20-441, approved 24 JUN 97). The original pharmacology/toxicology review for NDA 20-929 focused on inhalation findings not previously submitted. The present submission is a complete response to the Division's approvable letter dated May 20, 1998. It contains revised labeling and an inhalation toxicity study in young dogs beginning at age 2-weeks. A previous inhalation toxicity study was conducted by the applicant in young dogs beginning at about 5-weeks of age. The report of that study (#97058-1) was submitted and reviewed with the original NDA. Lung development is further progressed in dogs at 5-weeks than in humans at 6 months ( . Therefore, the Agency requested that the applicant conduct a study in younger dogs, whose stage of development might be closer to that of a 6-month-old human (see minutes of teleconference, January 15, 1997, IND 44,535). Labeling changes include: a)

# TOXICOLOGY

## General Toxicity of Budesonide Nebulizing Suspension Administered by the Inhalation Route to 2-Week Old Beagle Pups for a Period of 3 Months.

Astra Study 850-TO-0151, Report # SR97214-01, Volume 15.3, page 1

*Study Dates*: Experimental dates 10/22/97 – 01/23/98; Report issued 05/08/98
*Testing Lab:* [redacted]
*Test Article:* Budesonide nebulizing suspension, Batch/Lot: 41-01
*GLP:* The study was accompanied by a signed GLP statement.
*QA Report:* Yes (✓)/No ( )

**Methods:**

Male and female beagle pups (12-17 days old, 0.6-0.9 kg) were allotted to these groups:

| Group | No. and Sex | Formulation | Aerosol (mg/kg) | Budesonide (µg/kg) | Polysorbate 80 (µg/kg) |
|---|---|---|---|---|---|
| 1 | 4M/4F | Air Control | 0 | 0 | 0 |
| 2 | 4M/4F | I | 25 | 0 | 50 |
| 3 | 4M/4F | II | 25 | 2 | 5 |
| 4 | 4M/4F | III | 25 | 10 | 5 |
| 5 | 4M/4F | IV | 25 | 50 | 5 |

*Formulations*: (Differences among the 4 formulations are highlighted.)

| Formulation | I | II | III | IV |
|---|---|---|---|---|
| Batch number | DYG 68 | DYG 4 | DYH 7 | DYI 83 |
| Components (mg/mL) | | | | |
| Budesonide | 0 | 0.08 | 0.40 | 2.0 |
| $Na_2EDTA$ | [redacted] | | | |
| NaCl | | | | |
| Polysorbate 80 | | | | |
| Citric acid | | | | |
| Water | | | | |

About 10 days before whelping, bitches were moved into maternity cages in the research facility. Following whelping, pups from the same litter were housed together with the mother without consideration to dose group and sex. At about 6-weeks of age pups were weaned and housed together. Because of potential immunosuppression by the test article, pups were not vaccinated during the study. Pups were identified by litter and coat pattern until being tattooed in the ear with an identification number at about 5 weeks of age. Littermates were randomized to groups 2-5 with an attempt to balance the distribution of age and body weight. Group 1 animals (air controls) were from a single litter and so were not randomized. Aerosol exposure was via an [redacted] exposure chamber, with rubber dental dam collars for head-only exposure. To minimize stress, pups were

acclimated to placement within dental dam collars for 2-3 days before the first exposure. The eyes were protected from exposure to the test article by a combination of a protective ointment and custom-made eye goggles. Formulations were nebulized by an [redacted] Nebulizer. Based on online measurement of aerosol concentration (light scattering monitor) exposure duration was adjusted from 17 to 34 minutes to achieve the targeted exposure. Particle size distribution was determined by a cascade impactor; aerosol concentration was determined chemically from chamber samples collected daily. A chemical assay for polysorbate 80 was not available; it was determined by weight in samples from the vehicle group. Inhaled dose, total deposited dose, and pulmonary deposited dose were calculated from measured aerosol concentration, exposure time, and body weight, estimated respiratory minute volume (calculated from historical data), measured particle size, and separate total and pulmonary deposition factors for the fraction of drug collected on each stage of the cascade impactor. Respiratory minute volume was measured in other dogs in the colony of various ages using a facemask connected to a pneumotach. From those measured data, minute volume (MV) in the study dogs was estimated from body weight (x) using the following regression equations:

$$MV = 0.0558\ x^2 + 0.1656\ x + 0.3287 \text{ (males)}$$
$$MV = 0.0772\ x^2 + 0.2264\ x + 0.0386 \text{ (females)}$$

The deposition factors used were published values for human nose breathing shown in the table below. The overall deposition factors work out to ~47% for total deposition and ~13% for pulmonary deposition. The human values used by the applicant tend to be lower than the range of values reported for dogs (shown in parentheses) in a review of the literature review (*J. Toxicol. Environ. Health* 15:197, 1985). There are no published deposition factors for very young dogs and more emphasis should be placed on measured plasma concentrations for comparison of exposure with human pediatric patients.

**Deposition Factors Used by Investigators to Calculate Deposited Doses**

| Impactor Stage Number | Size Interval (μm) | Total Deposition (%) | Pulmonary Deposition (%) |
|---|---|---|---|
| 1 | [redacted] | 98 *(ND)* | 6 *(ND)* |
| 2 | [redacted] | 91 *(ND)* | 14 *(ND)* |
| 3 | [redacted] | 70 *(42-59)* | 18 *(19)* |
| 4 | [redacted] | 42 *(48-50)* | 15 *(24-34)* |
| 5 | [redacted] | 24 *(24-40)* | 12 *(27-30)* |
| 6 | [redacted] | 15 *(31-32)* | 11 *(28)* |
| 7 | [redacted] | 12 *(ND)* | 11 *(17-21)* |
| 8 | [redacted] | 13 *(32-52)* | 13 *(13-26)* |

Values in parentheses indicate range of published values for adult dogs; ND indicates no data available for that particle size range.

The following observations were made:

Clinical signs ..... observation for 30-60 minutes after dosing
Physical exam..... about every 2-weeks
Body weight..... daily
Development..... daily examination for eye opening, ear opening, and tooth eruption.
Food intake ..... not measured
Temperature..... rectal body temperature taken 3 times per week
EKG..... 10 lead electrocardiogram once in the week before termination
Ophthalmology..... prestudy, 1-month, and 3-months
Clinical pathology .. pre-study, week 3, and 3 months
Urinalysis..... pre-study, week 3, and 3 months
Adrenal function..... baseline and ACTH-stimulated plasma cortisol at 3-wk and 3-mo
Plasma drug levels.. 4-weeks at 0.25, 0.5,1, 2, 4, and 8 hr post-dose; 3-months at 0.25, 0.5, 1, 2, 4, 8, 16, and 24 hr post-dose.
Necropsy..... terminal
Histopathology ..... comprehensive list of tissues and macroscopic lesions were examined in all groups; see histopathology inventory.

**Results:** Summarized in Table 1 (*in vivo* findings) and Table 2 (*post mortem* findings)

*Mortality:* None
*Clinical Signs:* Inguinal hernia was seen in 1 male and 2 females at the high dose.
*Body Weight:* Body weight gain was decreased in a dose-related manner.
*Food Intake:* Not measured
*Developmental Landmarks:* The report states that there were no differences in the day of eye opening, ear opening, or tooth eruption but no data were presented to support the claim.

*Ophthalmoscopy:* No toxicologically significant treatment-related effects.

*Electrocardiography:* A veterinary cardiologist's statement indicates that EKGs were within normal limits; values for heart rates and EKG intervals were not reported.

*Adrenal Function:* Dose-related decreases were observed in baseline and ACTH-stimulated plasma cortisol. There was only modest, if any, increase in the degree of suppression from week 4 to week 12. Moderate suppression was apparent at the low dose; no statistical analysis was performed on the data.

*Hematology:* There were small increases in red cell count, hemoglobin, and hematocrit typically seen with glucocorticoids. These changes were not statistically significant; only hemoglobin is shown in Table 1 for illustration. At the high dose, the percentage of lymphocytes was decreased and the percentage of neutrophils increased (statistically significant only in males) with no overall effect on total white cell count.

**Table 1. In Vivo Findings in 3-month Inhalation Study in Young Pups**

| | | males | | | | | females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | air | vehicle | low | mid | high | air | vehicle | low | mid | high |
| Particle size MMAD (µm) | | --- | | | | | --- | | | | |
| Presented dose (µg/kg) | | --- | --- | 1.8 | 7.9 | 40.1 | --- | --- | 1.7 | 7.1 | 33.6 |
| Total deposited dose (µg/kg) | | --- | --- | 0.7 | 3.7 | 22.8 | --- | --- | 0.7 | 3.3 | 19.2 |
| Lung deposited dose (µg/kg) | | --- | --- | 0.2 | 1.1 | 5.6 | --- | --- | 0.2 | 1.0 | 4.7 |
| Inguinal hernia | | 0/4 | 0/4 | 0/4 | 0/4 | 1/4 | 0/4 | 0/4 | 0/4 | 0/4 | 2/4 |
| Body wt. gain wks 1-13 (kg) | | 5.4 | 5.7 | 4.6 | 4.2 | 4.3 | 5.3 | 4.9 | 4.3 | 3.6 | 2.7 |
| % Δ *vs* combined controls | | | | -17% | -25% | -23% | | | -16% | -31% | -47% |
| Basal | wk 4 | 11 | 41 | 41 | 46 | 5 | 12 | 35 | 21 | 65 | 6 |
| Cortisol (nM) | wk 12 | 107 | 80 | 48 | 19 | 5 | 58 | 15 | 28 | 11 | 5 |
| Average weeks 4-12 | | 59 | 61 | 45 | 33 | 5 | 35 | 25 | 25 | 38 | 6 |
| % Δ *vs* combined controls | | | | -26% | -46% | -92% | | | -18% | 27% | -82% |
| Post-ACTH | wk 4 | 169 | 190 | 188 | 94 | 12 | 210 | 248 | 202 | 116 | 15 |
| Cortisol (nM) | wk 12 | 242 | 237 | 205 | 111 | 12 | 276 | 263 | 215 | 121 | 26 |
| Average weeks 4-12 | | 206 | 214 | 197 | 103 | 12 | 243 | 256 | 209 | 119 | 21 |
| % Δ *vs* combined controls | | | | -6% | -51% | -94% | | | -16% | -52% | -92% |
| Hb (g/dL) | wk 4 | 8.9 | 8.1 | 8.5 | 8.6 | 9.3 | 8.8 | 9.1 | 9.3 | 9.0 | 9.6 |
| | wk 12 | 10.9 | 11.4 | 11.7 | 11.4 | 11.8 | 11.0 | 11.6 | 11.5 | 12.3 | 11.7 |
| Average weeks 4-12 | | 9.9 | 9.8 | 10.1 | 10.0 | 10.6 | 9.9 | 10.4 | 10.4 | 10.7 | 10.7 |
| % Δ *vs* combined controls | | | | 3% | 2% | 7% | | | 3% | 5% | 5% |
| Lymphocytes (%) | wk 4 | 43 | 38 | 41 | 39 | 29 | 48 | 45 | 44 | 35 | 33 |
| | wk 12 | 34 | 34 | 37 | 35 | 20 | 35 | 33 | 35 | 26 | 22 |
| Average weeks 4-12 | | 38 | 36 | 39 | 37 | 25 | 41 | 39 | 40 | 31 | 27 |
| % Δ *vs* combined controls | | | | 5% | -1% | -33% | | | -2% | -24% | -32% |
| Neutrophils (%) | wk 4 | 50 | 49 | 49 | 48 | 57 | 43 | 45 | 47 | 51 | 55 |
| | wk 12 | 57 | 56 | 52 | 54 | 68 | 55 | 57 | 55 | 63 | 64 |
| Average weeks 4-12 | | 53 | 53 | 50 | 51 | 63 | 49 | 51 | 51 | 57 | 59 |
| % Δ *vs* combined controls | | | | -5% | -4% | 18% | | | 2% | 15% | 19% |
| Alk. Phos. (IU/L) | wk 4 | 232 | 175 | 178 | 198 | 240 | 168 | 147 | 155 | 220 | 233 |
| | wk 12 | 216 | 237 | 280 | 282 | 286 | 191 | 206 | 223 | 317 | 264 |
| Average weeks 4-12 | | 224 | 206 | 229 | 240 | 263 | 180 | 177 | 189 | 269 | 249 |
| % Δ *vs* combined controls | | | | 7% | 12% | 22% | | | 6% | 51% | 40% |
| BUN (mg/dL) | wk 4 | 11 | 16 | 17 | 13 | 15 | 12 | 17 | 16 | 13 | 15 |
| | wk 12 | 12 | 10 | 12 | 16 | 21 | 11 | 12 | 14 | 14 | 21 |
| Average weeks 4-12 | | 12 | 13 | 15 | 15 | 18 | 12 | 15 | 15 | 14 | 18 |
| % Δ *vs* combined controls | | | | 18% | 18% | 47% | | | 15% | 4% | 38% |
| ALT (U/L) | wk 4 | 36 | 23 | 20 | 30 | 28 | 36 | 21 | 22 | 29 | 29 |
| | wk 12 | 47 | 43 | 32 | 35 | 33 | 45 | 35 | 34 | 34 | 29 |
| Average weeks 4-12 | | 42 | 33 | 26 | 33 | 31 | 41 | 28 | 28 | 32 | 29 |
| % Δ *vs* combined controls | | | | -30% | -13% | -18% | | | -18% | -8% | -15% |

Highlighted values indicate statistically significant difference vs control groups.

*Clinical Chemistry:* Several changes were seen that are typical of glucocorticoids but are not toxicologically significant. These include modest increases in alkaline phosphatase and BUN, with decreased ALT. Alkaline phosphatase enzyme activity is induced by corticosteroids. Increased BUN probably reflects altered protein metabolism; plasma creatinine was not affected and there were no histological effects in the kidney.

*Urinalysis:* No toxicologically significant treatment-related effects.

*Organ Weights:* Expected decreases were observed in relative weights of adrenals, thymus, lungs, and gonads. These changes were often not statistically significant due to the small number of animals and large inter-animal variation. There was only a slight trend for decreased spleen weight.

*Gross Pathology:* No toxicologically significant treatment-related effects.

*Histopathology:* Expected glucocorticoid effects included: a) adrenal cortical atrophy, b) atrophy of the skin, c) lymphoid depletion of thymus, ileum (Peyer's patches), spleen, and tonsils, and d) vacuolation of hepatocytes. Decreased cellularity of the bone marrow at the high dose is a finding that is occasionally seen with glucocorticoids. A differential count of bone marrow cells indicated an increased percentage of myeloid cells, particularly the proliferating cell types. This probably correlates with the observed increase in circulating neutrophils. No treatment related findings were reported for the respiratory tract. Most of the animals in all groups were observed to have "chronic inflammation" in the lung alveoli. There was no histological correlate for the decreased lung weight.

*Toxicokinetics:* Plasma concentrations increased with increasing dose. The increase was dose-proportional for females but less than dose-proportional in males. As expected in inhalation studies, there was substantial day to day variation in presented dose. AUC normalized for dose showed that systemic exposure tended to decrease from week 4 to week 12, and tended to be greater in males than in females. $C_{max}$ always occurred at the first time point measured after exposure (~15 minutes). AUC values at the low dose are relatively inaccurate because plasma concentrations were above the limit of quantitation at only a few time points.

**Table 2 Post-mortem and Toxicokinetic Results in 3-Month Inhalation Study**

| | males | | | | | females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | air | vehicle | low | mid | high | air | vehicle | low | mid | high |
| Presented dose (µg/kg) | --- | --- | 1.8 | 7.9 | 40.1 | --- | --- | 1.7 | 7.1 | 33.6 |
| Total deposited dose (µg/kg) | --- | --- | 0.7 | 3.7 | 22.8 | --- | --- | 0.7 | 3.3 | 19.2 |
| Lung deposited dose (µg/kg) | --- | --- | 0.2 | 1.1 | 5.6 | --- | --- | 0.2 | 1.0 | 4.7 |
| **Relative Organ Weights** (organ-to-brain ratio %) | | | | | | | | | | |
| Adrenal | 1.0 | 1.0 | 1.1 | 0.7 | 0.6 | 1.2 | 1.1 | 0.9 | 0.7 | **0.6** |
| % Δ *vs* combined controls | | | 14% | -24% | -41% | | | -24% | -42% | **-53%** |
| Thymus | 24.7 | 18.1 | 16.3 | 10.9 | **5.7** | 22.7 | 22.5 | 19.8 | 8.8 | 5.6 |
| % Δ *vs* combined controls | | | -24% | -49% | **-73%** | | | -12% | -61% | -75% |
| Spleen | 15.8 | 22.6 | 20.1 | 18.6 | 17.9 | 17.1 | 22.6 | 23.7 | 19.1 | 14.0 |
| % Δ *vs* combined controls | | | 5% | -3% | -7% | | | 19% | -4% | -29% |
| Lungs | 84.7 | 85.6 | 73.2 | 69.4 | **57.8** | 87.2 | 80.6 | 74.6 | 58.6 | 45.3 |
| % Δ *vs* combined controls | | | -14% | -18% | **-32%** | | | -11% | -30% | -46% |
| Testes/Ovaries | 1.8 | 1.8 | 1.6 | 1.6 | 1.4 | 0.7 | 0.8 | 0.7 | 0.6 | 0.5 |
| % Δ *vs* combined controls | | | -8% | -12% | -22% | | | -8% | -16% | -32% |
| **Histology** | | | | | | | | | | |
| Adrenal - cortical atrophy | 0/4 | 0/4 | 0/4 | 4/4 | 4/4 | 0/4 | 0/4 | 0/4 | 4/4 | 4/4 |
| Skin - atrophy | 0/4 | 0/4 | 0/4 | 0/4 | 2/4 | 0/4 | 0/4 | 0/4 | 0/4 | 2/4 |
| Thymus - atrophy | 0/4 | 0/4 | 0/4 | 4/4 | 3/3 | 0/4 | 0/4 | 0/4 | 1/4 | 3/3 |
| Ileum - lymphoid depletion | 0/4 | 0/4 | 0/4 | 4/4 | 3/4 | 0/4 | 0/4 | 1/4 | 4/4 | 3/4 |
| Spleen - lymphoid depletion | 0/4 | 0/4 | 0/4 | 0/4 | 1/4 | 0/4 | 0/4 | 0/4 | 1/4 | 3/4 |
| Liver - vacuolar change | 1/4 | 1/4 | 1/4 | 0/4 | 4/4 | 0/4 | 1/4 | 0/4 | 1/4 | 2/4 |
| Tonsil - lymphoid depletion | 0/4 | 0/4 | 0/4 | 0/4 | 1/4 | 0/4 | 0/4 | 0/4 | 0/4 | 2/4 |
| Bone Marrow | | | | | | | | | | |
| erythroid depletion | 0/4 | 0/4 | 0/4 | 0/4 | 1/4 | 0/4 | 0/4 | 0/4 | 0/4 | 2/4 |
| myeloid depletion | 0/4 | 0/4 | 0/4 | 0/4 | 1/4 | 0/4 | 0/4 | 0/4 | 0/4 | 2/4 |
| Total myeloid cells (%) | 54 | 56 | 58 | 57 | 61 | 55 | 55 | 55 | 58 | 60 |
| % proliferating myeloid | 11 | 10 | 17 | 18 | 19 | 11 | 15 | 16 | 19 | 18 |
| % non-proliferating myeloid | 43 | 46 | 42 | 39 | 41 | 45 | 40 | 39 | 39 | 42 |
| Myeloid/erythroid ratio | 1.1 | 1.2 | 1.4 | 1.3 | 1.5 | 1.2 | 1.2 | 1.2 | 1.3 | 1.5 |
| Presented dose (µg/kg) 1-mo | | | 1.2 | 11 | 28 | | | 1.2 | 11 | 28 |
| Cmax (nM) 1-mo | | | 1.79 | 11.2 | 24.9 | | | 0.47 | 5.48 | 13.3 |
| AUCtot (nmol·hr/L) 1-mo | | | 1.78 | 10.6 | 21.4 | | | 0.62 | 5.74 | 15.1 |
| AUC/dose 1-mo | | | 1.48 | 0.96 | 0.76 | | | 0.52 | 0.52 | 0.54 |
| Presented dose (µg/kg) 3-mo | | | 1.8 | 7.1 | 49 | | | 1.8 | 7.1 | 49 |
| Cmax (nM) 3-mo | | | 1.18 | 3.34 | 28.5 | | | 0.47 | 2.87 | 17.6 |
| AUCtot (nmol·hr/L) 3-mo | | | 1.42 | 3.69 | 27.3 | | | 0.76 | 4.33 | 21.6 |
| AUC/dose 3-mo | | | 0.79 | 0.52 | 0.56 | | | 0.42 | 0.61 | 0.44 |

Highlighted values indicate statistically significant difference vs control groups.

**Key Study Findings:** Budesonide suspension was administered for 3-months by head-only exposure to young dogs, beginning at an age of 2-weeks, at the following doses:

| Presented dose (µg/kg) | air | vehicle | 1.8 | 7.5 | 37 |
|---|---|---|---|---|---|
| Total deposited dose (µg/kg) | --- | --- | 0.7 | 3.5 | 21 |
| Lung deposited dose (µg/kg) | --- | --- | 0.2 | 1 | 5 |

Treatment related changes consisted of known glucocorticoid effects including: inguinal hernia, decreased body weight gain, decreased baseline and ACTH-stimulated plasma cortisol, decreased circulating lymphocytes with increased neutrophils, decreased organ weights of adrenals, thymus, gonads, and lung. Histological changes included: adrenal cortical atrophy, atrophy of the skin, lymphoid depletion of thymus, spleen, ileum (Peyer's patches), and tonsils, vacuolation of hepatocytes, and decreased cellularity of bone marrow. An absolute no effect level was not established. The low dose of 1.8 µg/kg was a threshold dose for effects on: body weight gain (17%↓ ♂, 16%↓ ♀), ACTH-stimulated cortisol (16%↓ ♀), adrenal weight (24%↓ ♀), and thymus weight (24%↓ ♂, 12%↓ ♀).

## Summary and Evaluation of Toxicology

Treatment related findings consisted of known glucocorticoid effects. Other than the decrease in lung weight, there were no specific effects on the respiratory tract. There were no effects attributable to the vehicle. The findings in this study were qualitatively and quantitatively similar to the previous 3-month study in slightly older pups (beginning at 5-6 weeks of age). A few key comparisons are summarized in Table 3, below; values are for males and females combined.

**Table 3. Comparison of Key Findings in 3-Month Immature Dog Studies**

| Starting Age | Presented Dose (µg/kg) | Plasma Budesonide Cmax* (nM) | Plasma Budesonide AUC* (nmol·h/L) | post ACTH cortisol (% Δ) | Relative Organ Weights adrenal (% Δ) | Relative Organ Weights thymus (% Δ) | Relative Organ Weights lung (% Δ) |
|---|---|---|---|---|---|---|---|
| 5-wk | 1.6 | 0.6 | 0.7 | -7 | -2 | 8 | -1 |
| | 8 | 2.2 | 2.4 | -48 | -29 | -25 | -3 |
| | 40 | 12.9 | 11.0 | -96 | -44 | -74 | -30 |
| 2-wk | 1.8 | 1.0 | 1.1 | -17 | -5 | -18 | -13 |
| | 7.5 | 5.7 | 6.1 | -54 | -33 | -55 | -24 |
| | 37 | 21.1 | 21.4 | -93 | -47 | -74 | -39 |

* average $C_{max}$ and $AUC_{tot}$ at 3-4 weeks and 11-12 weeks.

The younger pups may have been somewhat more sensitive to the treatment; the changes at the low and mid doses were consistently greater in the younger pups. However, the systemic exposures, as measured by $C_{max}$ or AUC, were also consistently greater in the younger pups. This suggests that actual lung deposition may have been greater in the

younger pups. The difference in exposure methods (face mask in the older pups, whole head exposure in the younger pups) might account for a difference in deposition. Visual inspection of the plasma concentration *vs* time curves did not indicate a change in elimination rate over time in either of the studies in young dogs. As noted in the review of the previous 3-month inhalation study in pups 5-weeks of age, immature dogs may be more sensitive to the effects of budesonide than older dogs. In the immature dogs clear dose-related systemic glucocorticoid effects were seen in the range of 8 to 40 µg/kg. In previous 6-week, 6-month, and 1-year studies in adult dogs similar effects were seen in the range of 60 to 200 µg/kg. However, the previous studies used different formulations (metered dose inhaler) and delivery systems which might account for an apparent difference in sensitivity. Toxicokinetics were not measured in the previous studies. As also noted in the previous review, young pups seem to be more sensitive to the systemic effects of budesonide than are human children. Data from the human PK summary in the original NDA submission indicate that clinically well tolerated doses in children (3-6 years old) produced plasma AUCs of ~5 nmol·hr/L. In young dogs plasma AUCs > 2 nmol·hr/L were associated with marked systemic glucocorticoid effects.

In summary, all of the treatment related effects in very young pups were expected glucocorticoid effects. Effects in dogs treated from age 2-weeks were qualitatively similar to those in dogs treated from age 5-weeks, but the younger dogs may have been slightly more sensitive than the older pups. Most of the glucocorticoid effects can be monitored clinically. The decrease in lung weight would not be easily monitored clinically but, in both 3-month dog studies, the decrease in lung weight occurred only at doses that caused substantial adrenal suppression and lymphoid depletion that would probably not be clinically tolerated in humans. Thus, the present study in very young dogs, beginning at 2-weeks of age, does not raise any unique concerns for use of budesonide in infants age 6-month and older.

## LABELING REVIEW

The [redacted], require changes in the human exposure multiples for preclinical data in the labeling. As noted in the original review of this NDA, there are no suitable PK data for expressing animal exposures as multiples human AUC. Thus, dose multiples must be expressed on a mg/m² basis. Labeling calculations are presented in Table 4, page 10.

**Table 4. Dose Multiple Calculations for Labeling**

Drug: **Pulmicort Respules (10 kg child - labeled dose)**

| | age | mg/dose | # daily doses | mg/day | kg | mg/kg | factor | mg/m² |
|---|---|---|---|---|---|---|---|---|
| Pediatric | 1 | 0.5 | 2 | 1 | 10 | 0.10 | 25 | 2.50 |
| Adult | >12 | 0.5 | 2 | 1 | 50 | 0.02 | 37 | 0.74 |

| | route | mg/kg/d | conv. factor | mg/m² | Dose Ratio Adults | Dose Ratio Children | Rounded Dose Ratio Adults | Rounded Dose Ratio Children |
|---|---|---|---|---|---|---|---|---|
| Carcinogenicity: | | | | | | | | |
| mouse | po | 0.20 | 3 | 0.6 | 0.81 | 0.24 | 1/1 | 1/4 |
| rat | po | 0.05 | 6 | 0.3 | 0.41 | 0.12 | 1/2 | 1/8 |
| rat | po | 0.025 | 6 | 0.15 | 0.20 | 0.06 | 1/5 | 1/17 |
| rat | po | 0.01 | 6 | 0.06 | 0.08 | 0.02 | 1/12 | 1/42 |
| extra | | | — | — | — | — | — | — |
| Reproduction and Fertility: | | | | | | | | |
| rat | sc | 0.02 | 6 | 0.12 | 0.16 | N/A | 1/6 | N/A |
| rat | sc | 0.005 | 6 | 0.03 | 0.04 | N/A | 1/25 | N/A |
| rat | | | 6 | 0 | — | N/A | — | N/A |
| extra | | | — | — | — | N/A | — | N/A |
| Teratogenicity: | | | | | | | | |
| rabbit | sc | 0.025 | 12 | 0.3 | 0.41 | N/A | 1/2 | N/A |
| rat | sc | 0.5 | 6 | 3 | 4.05 | N/A | 4.0 | N/A |
| rat | inhalation | 0.25 | 6 | 1.5 | 2.03 | N/A | 2 | N/A |
| extra | | | — | — | — | N/A | — | N/A |
| extra | | | — | — | — | N/A | — | N/A |
| Overdosage: | | | | | | | | |
| mouse | inhalation | 100 | 3 | 300 | 405.41 | 120.00 | 410 | 120 |
| rat | inhalation | 68 | 6 | 408 | 551.35 | 163.20 | 550 | 160 |
| mouse | po | 200 | 3 | 600 | 810.81 | 240.00 | 810 | 240 |
| rat | po | 100 | 6 | 600 | 810.81 | 240.00 | 810 | 240 |

**Labeling Recommendations:**

1. The heading **"Carcinogenesis, Mutagenesis, Impairment of Fertility"** is missing from the draft labeling and should be inserted.

2. No changes are recommended in the dose multiples in the carcinogenicity and fertility sections because with the new calculations the multiples remain "less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis".

3. The "Pregnancy Category C:" section should be changed to read as follows (changes highlighted):

> Pregnancy Category C: As with other ——————— , budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a mcg/m $^2$ basis) and 500 mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m$^2$ basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 2 times the maximum human daily inhalation dose in adults on a mcg/m$^2$ basis).

1. The "Overdosage" section should be changed to read as follows (changes highlighted):

> In mice the minimal lethal inhalation dose was 100 mg/kg (approximately 10 or 120 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mcg/m$^2$ basis). In rats there were no deaths at an inhalation dose of 68 mg/kg (approximately 50 or 160 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mcg/m$^2$ basis). In mice the minimal oral lethal dose was 200 mg/kg (approximately 10 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mcg/m$^2$ basis). In rats, the minimal oral lethal dose was less than 100 mg/kg (approximately 10 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mcg/m$^2$ basis).

[redacted] No chemistry consult has been received regarding [redacted] from the

## RECOMMENDATIONS

1. The recommended labeling changes should be communicated to the sponsor.
2. The application is approvable from a preclinical viewpoint.

/S/ 04-Dec-98

Mark Vogel, Ph.D., Pharmacologist

/S/ Dec. 4, 1998

Original NDA 20-929
c.c. HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/W.M. Vogel
HFD-570/S. Chu
HFD-570/G. Trout

**Histopathology Inventory for NDA 20-929 (organ weights obtained for highlighted tissues)**

| Species<br>Duration<br>Route<br>Formulation<br>Report # | young rat<br>1-month<br>inhalation<br>suspension<br>96249-1 | 5 wk old dog<br>3-month<br>inhalation<br>suspension<br>97058-1 | rat<br>6-month<br>inhalation<br>suspension<br>97071-1 | 2 wk old dog<br>3-month<br>inhalation<br>suspension<br>97214-1 |
|---|---|---|---|---|
| Adrenals | ✓ | ✓ | ✓ | ✓ |
| Aorta | | | ✓ | |
| Bone Marrow smear | ✓ | ✓ | ✓ | ✓ |
| Bone (femur) | ✓ | ✓ | | |
| Brain | ✓ | ✓ | ✓ | ✓ |
| Colon | ✓ | ✓ | ✓ | ✓ |
| Duodenum | ✓ | ✓ | ✓ | ✓ |
| Epididymis | ✓ | ✓ | ✓ | ✓ |
| Esophagus | ✓ | ✓ | ✓ | ✓ |
| Eye | ✓ | ✓ | ✓ | ✓ |
| Gall bladder | | ✓ | | ✓ |
| Harderian gland | | | ✓ | |
| Heart | ✓ | ✓ | ✓ | ✓ |
| Ileum | ✓ | ✓ | ✓ | ✓ |
| Jejunum | ✓ | ✓ | | ✓ |
| Kidneys | ✓ | ✓ | ✓ | ✓ |
| Lachrymal gland | | | ✓ | |
| Larynx | ✓ | ✓ | ✓ | ✓ |
| Liver | ✓ | ✓ | ✓ | ✓ |
| Lymph node, axillary | ✓ | ✓ | ✓ | ✓ |
| Lymph node, mesenteric | ✓ | ✓ | ✓ | ✓ |
| Lungs | ✓ | ✓ | ✓ | ✓ |
| Mammary Gland | ✓ | ✓ | | Females |
| Nasal cavity | ✓ | ✓ | ✓ | ✓ |
| Optic nerves | ✓ | ✓ | ✓ | ✓ |
| Ovaries | ✓ | ✓ | ✓ | ✓ |
| Pancreas | ✓ | ✓ | ✓ | ✓ |
| Parathyroid | ✓ | ✓ | ✓ | ✓ |
| Peripheral nerve | ✓ | ✓ | ✓ | ✓ |
| Pharynx | | | ✓ | |
| Pituitary | ✓ | ✓ | ✓ | ✓ |
| Prostate | ✓ | ✓ | ✓ | ✓ |
| Salivary gland | ✓ | ✓ | ✓ | ✓ |
| Seminal vesicles | ✓ | | ✓ | |
| Skeletal muscle | ✓ | ✓ | ✓ | ✓ |
| Skin | ✓ | ✓ | ✓ | ✓ |
| Spinal cord | | | ✓ | |
| Spleen | ✓ | ✓ | ✓ | ✓ |
| Stomach | ✓ | ✓ | ✓ | ✓ |
| Testes | ✓ | ✓ | ✓ | ✓ |
| Thymus | ✓ | ✓ | ✓ | ✓ |
| Thyroid | ✓ | ✓ | ✓ | ✓ |
| Tongue | | | ✓ | |
| Trachea | ✓ | ✓ | ✓ | ✓ |
| Urinary Bladder | ✓ | ✓ | ✓ | ✓ |
| Uterus | ✓ | ✓ | ✓ | ✓ |
| Vagina | ✓ | ✓ | ✓ | ✓ |
| Preputial/clitoral gland | | | ✓ | |
| Other | carina | soft palate | oviduct | soft palate |
| Other | | carina | | carina |
| Other | | bronchus | | bronchus |
| Other | | rib | | |

T/cout

APR 28 1998

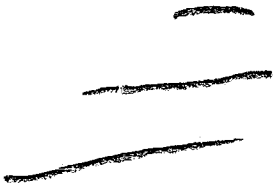
# REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Original Review

| | |
|---|---|
| **KEY WORDS:** | Reformulation, pharmacology, pharmacokinetics, inhalation toxicology |
| **Reviewer Name:** | W. Mark Vogel, Ph.D. |
| **Division Name:** | Division of Pulmonary Drug Products |
| **HFD#:** | HFD-570 |
| **Review Completion Date:** | 28 April, 1998 |
| **Electronic File Number:** | not applicable |
| **NDA Number:** | 20-929 |
| **Serial Number:** | 000 |
| **Submission Dates:** | 18 NOV 97, 15 JAN 98 |
| **Submission Type:** | Original NDA |
| **Information to Sponsor:** | Yes (✓), No ( ) |
| **Sponsor or Agent:** | Astra USA Inc., Westborough, MA |

**Drug:**

| | |
|---|---|
| *Code Name:* | S-1320 (RS) S-1322 (R) S-1321 (S) |
| *Generic Name:* | Budesonide nebulizing suspension |
| *Trade Name:* | Pulmicort Respules™ |
| *Chemical Name:* | (RS)11β,16α17,21,tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde |
| *CAS Registry Number:* | 51333-22-3 |
| *Molecular Formula:* | $C_{25}H_{34}O_6$ |
| *Molecular Weight:* | 430.5 |
| *Structure:* | |



**Relevant INDs/NDAs:**

IND 21,632 & NDA 20-233 Astra, Rhinocort (budesonide) Nasal Inhaler
IND 31,308 & NDA 20-441 Astra, Pulmicort (budesonide) Turbuhaler
IND 44,535 Astra, Budesonide Nebulizer solution

**Previous Review:** None for this NDA
NDA 20-233, 23 JUL 93, Conrad H. Chen, Ph.D.
NDA 20-441, 11 JUN 96, Lawrence F. Sancilio, Ph.D., Luqi Pei, Ph.D.
Report of the Carcinogenicity Assessment Committee, 9/3/93
IND 44,535, serial N132, submitted 21 APR 1996, Reviewed by S. Tripathi, 30 SEP 1997

**Drug Class:**. Glucocorticoid steroid
**Indication:** Asthma

**Clinical Formulation (and components):** Drug is formulated as a sterile suspension of budesonide in aqueous vehicle for delivery by nebulizer. Unit doses are packaged in individual [redacted] ampules in [redacted] different strengths; each ampule contains 2 mL of suspension.

| | [redacted] | 0.5 mg/2mL | 1.0 mg/2mL |
|---|---|---|---|
| | [redacted] | mg/mL | mg/mL |
| Budesonide (micronized) | [redacted] | 0.25 | 0.5 |
| Edetate disodium ( [redacted] , USP | [redacted] | | |
| Sodium chloride, USP | | | |
| Polysorbate 80, NF | | | |
| Citric acid ( [redacted] , USP | | | |
| Sodium citrate, USP | | | |
| Water for injection, USP | | | |

**Route of Administration:** Oral Inhalation

**Studies Reviewed within this Submission:**
(Except where noted, studies are from the original submission of 18 NOV 97.)

**Nonclinical Pharmacology Astra Study Reports**

1. Sephadex-induced edema in the rat lung; Effects of D5171, D5330 and budesonide after repeated inhalation. Astra Draco Report 850-RD-0249. 1986. **vol 9/pg 130**
2. Intratracheally administered glucocorticosteroids inhibit LPS-induced TNF-α release from rat alveolar macrophages in vitro. A preliminary report. Astra Draco Report 850-RD-0342. **vol 9/pg 139**

**Nonclinical Pharmacology Publications and References**

3. Ryrfeldt A, Andersson PH, Edsbacker S et al. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. Eur J Respir Dis 1982; 63 (suppl 122):86-95. **vol 9/pg 151**
4. Wurthwein G, Rehder S, Rohdewald P. Lipophilicity and receptor affinity of glucocorticoids. Pharm Ztg Wiss 1992; 137:161-167. **vol 9/pg 162**
5. Astra Draco Analytical Record 1997-242D. **vol 9/pg 169**
6. Brattsand R. What factors determine anti-inflammatory activity and selectivity of inhaled steroids? Eur Resp Review 1997, in press. **vol 9/pg171**
7. Spahn JD, Landwehr LP, Nimmagadda S et al. Effects of glucocorticoids on lymphocyte activation in patients with steroid-sensitive and steroid-resistant asthma. J Allergy Clin Immunol 1996;98:1073-1079. **vol 9/pg177**

8. Korn SH, Wouters EFM, Wesseling G et al. In vitro and in vivo modulation of α- and β-glucocorticoid receptor mRNA in human bronchial epithelium. Am I Respir Crit Care Med 1997; 155:1117-1122. **vol 9/pg184**

9. Korn SH, Engel GEJ, Koerts-de-Lang E et al. α- and β–glucocorticoid receptor mRNA expression in rat lung and gastrocnemius after intra-tracheal instillation of budesonide. Am J Respir Crit Care Med 1997; 155 (No. 4 Pt 2):A358. **vol 9/pg 190**

10. Brattsand R, Axelsson B. Basis of airway selectivity of Inhaled Glucocorticoids. In: Inhaled Glucocorticoids in Asthma, Mechanisms and Clinical Action. Eds: Schleimer RP, Busse WW, O'Byrne PM. Dekker, New York, 1997, pp 351-380. **vol 9/pg 191**

11. Edsbacker S, Szefler SJ. Glucocorticoid pharmacokinetics: principles and clinical applications. In: Inhaled Glucocorticoids in Asthma, Mechanisms and Clinical Action. Eds: Schleimer RP, Busse WW, O'Byrne PM. Dekker, New York, 1997, pp 381-446. **vol 9/pg 220**

12. Miller-Larsson A, Hjertberg E, Mattsson H et al. Reversible fatty acid conjugation of budesonide results in a prolonged retention in airway tissue as compared to fluticasone propionate. Am J Respir Crit Care Med 1997; 155 (No 4 Pt 2):A353. **vol 9/pg 287**

13. Wieslander E, Delander EL, Jarkelid L et al. Reversible fatty acid conjugation of budesonide results in prolonged antiinflammatory activity in vitro as compared to fluticasone propionate. Am J Respir Crit Care Med 1997; 155 (No. 4 Pt 2):A353. **vol 9/pg 288**

14. Miller-Larsson A, Jansson P, Runstrom A et al. Reversible fatty acid conjugation of budesonide results in a prolonged topical anti-inflammatory activity in airways as compared to fluticasone propionate. Am J Respir Crit Care Med 1997; 155 (No. 4 Pt 2):A353. **vol 9/pg 289**

15. Hogger P, Erpenstein U, Sorg C et al. Receptor affinity, protein expression and clinical efficacy of inhaled glucocorticoids Am J Respir Crit Care Med 1996; 153 (No. 4 Pt 2):A222. **vol 9/pg 290**.

16. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids . J Allergy Clin Immunol 1996; 97:169-176. **vol 9/pg 291**

17. Hogger P, Rohdewald P. Binding kinetics of fluticasone propionate to the human glucocorticoid receptor. Steroids 1994; 59:597-602. **vol 9/pg 299**

18. McFadden ER. Budesonide Turbuhaler once daily administration for patients with mild-to-moderate chronic asthma. Am J Respir Crit Care Med 1997; 155 (No. 4 Pt 2):A352. **vol 9/pg 305**

19. McKay D, Brattsand R, Wieslander E et al. Budesonide inhibits T-cell-initiated epithelial pathophysiology in an in vitro model of inflammation. J Pharmacol Expl Ther 1996; 277:403-4 1 0. **vol 10/pg 1**

20. Oddera S, Silvestri M, Sacco O et al. Effects of "systemic" budesonide concentrations on in vitro allergen-induced activation of blood mononuclear cells isolated from asthmatic patients. Allergy 1995; 50:397-404. **vol 10/pg 9**

21. Lantero S, Sacco O, Scala C et al. Eosinophil locomotion and the release of IL-3 and IL-5 by allergen-stimulated mononuclear cells are effectively downregulated in vitro by budesonide. Clin Exp Allergy 1996; 26:656-664. **vol 10/pg 17**

22. Schmidt J, Fleissner S, Heimann-Weitschat I et al. The effect of different corticosteroids and cyclosporin A on interleukin-4 and interleukin-5 release from murine T(h)2-type T cells. Eur J Pharmacol 1994; 260:247-250. **vol 10/pg 27**

23. Debets JMH, Ruers TJM, van der Linden MPMH et al. Inhibitory effect of corticosteroids on the secretion of tumour necrosis factor (TNF) by monocytes is dependent on the stimulus inducing TNF synthesis. Clin Exp Immunol 1989; 78:224-229. **vol 10/pg 31**

24. Snijdewint FGM, Kapsenberg ML, Wauben-Penris P et al. Corticosteroids class-dependently inhibit in vitro Th1- and Th2- type cytokine production. Immunopharmacology 1995; 29:93-101. **vol 10/pg 37**

25. Schmidt J, Fleissner S, Heimann-Weitschat I et al. Pharmakologische Modulation der Cytokinproduktion von Murinen Th-2-Lymphocyten in vitro. Atemwegs Lungenkrankh 1995; 21:296-297. **vol 10/pg 46**

26. Ek A, Larsson B-M, Palmberg L et al. Glucocorticoids inhibit the release of cytokines from epithelial cells. Eur Resp J 1996; 9 (suppl 23):126. **vol 10/pg 53**

27. Mio L Adachi Y, Striz I et al. Retinoic acid and corticosteroids differently modulate IL-6 and IL-8 release from human bronchial epithelial cells. Am J Respir Crit Care Med 1996; 153:4 (No.4 Pt 2) A729. **vol 10/pg 54**

28. Roca-Ferrer J, Xaubet A, Mullol J et al. Topical steroids and nedocromil sodium inhibit GM-CSF release from healthy and inflamed human respiratory epithelial cells. Eur Resp J 1996; 9 (suppl 23):125 s. **vol 10/pg 55**

29. Xnubet A, Mullol J, Roca-Ferrer J et al. Effects of topical steroid on cytokine release from human nasal epithelial cells in vitro. Am J Respir Crit Care Med 1995; 151 (No. 4 pt 2): A367. **vol 10/pg 56**

30. Marianayagam L, Poulter LW, Corticosteroid can alter antigen expression on alveolar macrophages. Clin Exp Immunol 1991; 85:531-5. **vol 10/pg 57**

31. Borson DB, Gruenert DC. Glucocorticoids induce neutral endopeptidase in transformed human tracheal epithelial cells. Am J Physiol 199 1; 260:L83-L89. **vol 10/pg 62**

32. Proud D, Subauste MC, Ward PE. Glucocorticoids do not alter peptidase expression on a human bronchial epithelial cell line. Am J Respir Cell Mol Biol 1994; 11:57-65. **vol 10/pg 69**

33. Oddera S, Silvestri M, Sacco O et al. Evaluation of the inhibitory effects of budesonide on the mitogen-induced or the allergen-induced activation of blood mononuclear cells isolated from asthmatic patients. Ann Allergy Asthma Immunol 1995; 75: 33-40. **vol 10/pg 79**

34. Corrigan CJ, Bungre JK, Assouft B et al. Glucocorticoid resistant asthma: T-lymphocyte steroid metabolism and sensitivity to glucocorticoids and immunosuppressive agents. Eur Resp J 1996; 9:2077-2086. **vol 10/pg 87**

35. van Ierssel GJ, Mieremet-Ooms MA, van der Zon AM et al. Effect of cortisol and ACTH on corticosteroid-suppressed peripheral blood natural killer cells from healthy volunteers and patients with Crohn's disease. Immunopharmacology 1996; 34:97-104. **vol 10/pg 97**

36. Roca-Ferrer J, Mullol J, Lopez E et al. Effect of topical anti- inflammatory drugs on epithelial cell-induced eosinophil survival and GM-CSF secretion. Eur Respir J 1997; 10: 1489-1495. **vol 10/pg 106**

37. Denburg JA, Woolley M, Leber B et al. Basophil and eosinophil differentiation in allergic reactions. J Allergy Clin Immunol 1994; 94:1135-114 1. **vol 10/pg 113**

38. Piacentini GL, Mazzi P, Vinco S et al. The effect of budesonide on integrin-induced eosinophil activation. Eur Respir J 1994; 7 (suppl 18):70s. **vol 10/pg 120**

39. Striz I, Takigawa K, Romberger JD et al. Budesonide inhibition of TNFa-induced ICAM-1 expression on human bronchial epithelial cells. Am J Respir Crit Care Med 1996; 153: (No. 4 Pt 2):A26. **vol 10/pg 121**

40. Scordamaglia A, Paolieri F, Battifora M et al. Budesonide in vitro activity on a human continuous bronchial cell line: expression of ICAM-1. Allergy 1995; 50 (suppl 26):266. **vol 10/pg 122**

41. Kaiser J, Bickel CA, Bochner BS et al. The effects of the potent glucocorticoid budesonide on adhesion of eosinophils to human vascular enclothelial cells and on endothelial expression of adhesion molecules. J Pharmacol Exp Ther 1993; 267:245-249. **vol 10/pg 124**

42. Stellato C, Bech L, Gorgone GA et al. Expression of the chemokine RANTES by a human bronchial epithelial cell line. Modulation by cytokines and glucocorticoids. J Immunol 1995; 155:410-418. **vol 10/pg 129**

43. Stellato C, Collins P, Ponath PD et al. Production of the novel C-C chemokine MCP-4 by airway cells and comparison of its biological activity to other C-C chemokines. J Clin Invest 1997; 99:926-936. **vol 10/pg 139**

44. Brattsand R, Delander EL, Peterson C et al. Cytotoxicity of human phagocytes studied in vitro in a novel model based on Neutral Red absorbtion. Agents Actions 1991; 34:35-37. **vol 10/pg 152**

45. Tremblay GM, Nonaka M, Samstrand B et al. Myofibroblast differentation in nasal polyposis: Down-regulation by topical steroids. Can Respir J 1997; 4:205-2 10. **vol 10/pg 155**

46. Kassel O, Duvernelle C, Massart G et al, Corticosteroids inhibit expression of mast cell growth factor SCF in human lung fibroblasts in culture. Am J Respir Crit Care Med 1997; 155 (part 2 of 2 parts):A290. **vol 10/pg 156**

47. Dahlback M, Brattsand R, Kallstrom L et al. Inhalation of glucocorticoid particles (GCS) (budesonide) to the rat lung to prevent lung edema formation. J Aerosol Sci 1984; 15(3):218-219. **vol 10/pg 157**

48. Eirefelt S, Nerbrink 0, Kallstrom L et al. Anti-inflammatory effect of budesonicle; differences between intratracheal instillation and aerosol administration in Sephadex-induced lung edema in rats. J Aerosol Med 1994; 6:80. **vol 10/pg 158**

49. Nilsson M, Aberg P, Erjefalt S et al. Effect of insulated budesonide (BUD) powder on allergen challenge-induced late phase inflammatory exudation (LPE) in rat large airways. Am J Respir Crit Care Med 1997; 155 (No. 4 Pt 2):A879. **vol 10/pg 159**

50. Hayes JP, Barnes PJ, Newman Taylor AJ et al. Effect of a topical corticosteroid on airway hyperresponsiveness and eosinophilic inflammation induced by trimellitic anhydride exposure in sensitized guinea pigs. J Allergy Clin Immunol 1993; 92:450-456. **vol 10/pg 160**

51. Gozzard N, El-Hashim A, Herd CM et al. Effect of the glucocorticosteroid budesonide and a novel phosphodiesterase type 4 inhibitor CDP840 on antigen-induced airway responses in neonatally immunised rabbits. Br J Pharmacol 1996; 11 8:1201-1208. **vol 10/pg 168**

52. Denburg J, Woolley MJ, Ellis R et al. Allergen-induced changes in bone marrow progenitors and airway responsiveness in dogs. Int Arch Allergy Immunol 1995; 107:239-241. **vol 10/pg 176**

53. Inman MD, Ellis R, Wattie J et al. Effects of inhaled and systemic budesonide on allergen induced airway and bone marrow responses in dogs. Eur Resp J 1997. **vol 10/pg 179**

54. Stevens WHM. Adelroth E, Wattie J et al. Effect of inhaled budesonide on ozone-induced airway hyperresponsiveness and bronchoalveolar lavage cells in dogs. J Appl Physiol 1994; 77:2578-2583. **vol 10/pg 180**

55. Stevens WHM. Adelroth E, Woolley M et al. The effects of an inhaled corticosteroid on oxygen radical production by bronchoalveolar cells after allergen or ozone in dogs. Eur J Pharmacol Environ Toxicol Pharmacol section 1995, 293:251-257. **vol 10/pg 186**

56. Fornhem C, Dahlback M, Kumlin M et al. Effects of local and systemic budesonide on allergen-induced airway reactions in the pig. Br J Pharmacol 1996; 118:989-997. **vol 10/pg 193**

57. O'Riordan TG, Waldrep JC, Abraham WM et al. Effects of delivery of aerosolized budesonide to the respiratory tract of allergic sheep by liposomes. Am J Respir Crit Care Med 1996; 153 (part 2 of 2 parts): A336. **vol 10/pg 203**

58. O'Riordan TG, Otero RA, Lopez MJ et al. Anti-protease agents or corticosteroids can reverse antigen induced impairment of mucociliary clearance in ovine airways. Am J Respir Crit Care Med 1997; 155 (part 2):A878. **vol 10/pg 204**

59. Xu LJ, Olivenstein R, Martin JG et al. Effects of inhaled budesonide on allergen-induced airway narrowing, airway inflammation and leukotriene synthesis in rats. Am J Respir Crit Care Med 1995; 151 (No 4, pt 2):A223. **vol 10/pg 205**

60. Erjefalt J, Persson CGA. Effect of budesonide on allergen- and toluenediisocyanate-induced late phase airway exudation of bulk plasma. Am J Respir Crit Car Med 1995; 151 (No 4, pt 2): A223. **vol 10/pg 206**

61. Bacci E, Bertrand C, Geppetti P et al. Budesonide inhibits plasma extravasation induced by capsaicin and by substance P in the rat nasal mucosa. Regul Pept 1993; 49:159-166. **vol 10/pg 207**

62. Rado V, Boschetto P, Zancuoghi G et al. Effect of instilled budesonide on PAF-induced microvascular leakage in rat airways. Eur Respir J 1994; 7 (Suppl 18):383 s. **vol 10/pg 216**

63. Malm M, Engholm H, Andersson SE et al. Regulatory role of budesonide on leukocyte recruitment, granuloma formation and TNFα-release in sephadex-particle induced lung inflammation in rat. Am J Respir Crit Care Med 1997; 155 (part 2):A621. **vol 10/pg 217**

64. Andersson SE, Zackrisson C, Hemsen A et al. Regulation of lung endothelin content by the glucocorticosteroid budesonide. Biochem Biophys Res Commun 1992; 188:1116-112 1. **vol 10/pg 218**

65. Andersson SE, Eirefelt S, Zackrisson C et al. Regulatory effects of aerosolized budesonide and adrenalectomy on the lung content of endothelin-1 in the rat. Respiration 1995; 62:34-39. **vol 10/pg 224**

66. Miller-Larsson A, Runstrom A, Jansson P et al. Topical budesonide reverses the potentiation of late TNFα release in the airways of adrenalectomized rats. Am J Respit Crit Care Med 1997; 155 (No. 4 Pt 2):A879. **vol 10/pg 230**

67. Rylander R, Marchat B. Modulation of acute endotoxin pulmonary inflammation by a corticosteroid. J Clin Lab Immunol 1988; 27:83-86. **vol 10/pg 231**

68. Izumi T, Bakhle YS. Modification by steroids of pulmonary oedema and prostaglandin E2 pharmacokinetics induced by endotoxin in rats. Br J Pharmacol 1988; 93:955-963. **vol 10/pg 234**

69. Erjefalt J, Erjefalt I, Sundler F et al. Effects of topical budesonide on epithelial restitution in vivo in guinea pig trachea. Thorax 1995; 50:785-792. **vol 10/pg 243**

70. Miller Larsson A, Jansson P, Brattsand R et al. Selective tracheo-bronchial lavage in the rat - a method allowing characterization of airway inflammation without involvement of the alveolar compartment. Am J Respir Crit Care Med 1997; 155 (part 2):A619. **vol 10/pg 251**

71. Wiesenberg I, Pignat W, Anderson GP. $\beta_2$-adrenoceptor agonist- steroid interactions in murine eosinophilic lung inflammation in vivo. Am J Respir Crit Care Med 1997; 155 (No. 4 Pt 2):A736. **vol 10/pg 252**

72. O'Byrne P, Barnes PJ, Lofdahl CG et al. Additive effects of budesonide and formoterol in reducing severe asthma exacerbations over 12 months. Am J Respir Crit Care Med 1997; 155 (No. 4 Pt 2):A349. **vol 10/pg 253**

**New Toxicology Studies Not Previously Submitted to IND 44,535**

73. General Toxicity of Budesonide given to Young Rats by the Inhalation Route for 1 Month, report #96249-1, 850-TO-0147, **vol 11/pg 039**

74. General Toxicity of Budesonide Nebulizing Suspension given to Young Dogs by the Inhalation Route for 3 Months, study # 97058-1, **vol 12/pg 258**

75. General Toxicity Study of Budesonide Nebulizing Suspension and Polysorbate 80 — Potassium Sorbate Given to Young Rats by the Inhalation Route for 6 Months, # 850-RD-043 (toxicokinetics) **vol 6.3/pg 001**,, #850-TO-0149 (toxicology), **vol 6.3/pg 022**, submission of 15 JAN 98.

**New Pharmacokinetics (ADME) Studies**

76. Pharmacokinetic Study of Budesonide. Budesonide Concentration in Plasma. Astra Draco Report No. 850-RD-0391 **vol 16/pg 041**

77. General Toxicity and Recovery in Rats Given Budesonide by the Inhalation Route for 4 Weeks. Plasma Concentration Study. Astra Draco Report No. 850-RD-0390 **vol 16/pg 070**

78. General Toxicity of Budesonide Given to Young Rats by the Inhalation Route for 1 Month. Plasma Concentration Study. Astra Draco Report 850-RD-0397, 1997. **vol 16/pg 098**

79. Bioavailability of Inhaled Nebulised Suspension or Dry Powder Formulation of Budesonide, in Intubated Beagle Dogs. Astra Draco Report 850-RD-0402, 1997 **vol 16/pg 121**

80. Toxicity of Budesonide Nebulising Suspension Given to Young Immature Dogs by the Inhalation Route for 3 Months. Plasma Concentration Study. Astra Draco Report 850-RD-0401, 1997. **vol 16/pg 152**

**Pharmacokinetic (ADME) Publications or References**

81. Pacifici GM, Ferroni MA, Ternellini A, Gucci A, Morelli MC, Giuliani L. Human liver budesonide sulphotransferase is inhibited by testosterone and correlates with testosterone sulphotransferase. Eur. J. Clin. Pharmacol 1994; 46:49-54. **vol 16/pg 176**

82. Wurthwein G, Rehder S, Rohdewald P. Lipophilicity and receptor affinity of glucocorticoids. Pharm. Ztg. Wiss 1992; 137:161-167. **vol 16/pg 182** (reviewed in Pharmacology section)

**Studies Previously Reviewed:** Toxicology Studies also Submitted to IND 44,535, serial N132 on April 21, 1996 Reviewed by S. Tripathi, September 30, 1997

83. Dose Finding Study of Budesonide given to Rats for 14 Days by the Inhalation Route T3260,850-TO-0145 **vol 14/pg 001**

84. General Toxicity and Recovery in Rats given Budesonide by the Inhalation Route for 4 Weeks T3289,850-TO-0146 1.14 152 **vol 14/pg 152**

**Studies Not Reviewed within this Submission:** None

*Note: Portions of this review were excerpted directly from the sponsor's submission.*

**Introduction/Drug History:** Budesonide is approved for nasal inhalation in allergic rhinitis (Rhinocort, NDA 20-233, approved 14 FEB 97) and as a dry powder inhaler for asthma (Pulmicort Turbuhaler, NDA 20-441, approved 24 JUN 97). The present application focuses on recent inhalation findings not previously submitted

## PHARMACOLOGY

The sponsor has submitted two new Astra study reports and numerous nonclinical pharmacology reports and reviews from the published literature. These reports are summarized in Tables 1-4 and figure 1 on pages 9-12.

*MECHANISM OF ACTION:*

Budesonide is a glucocorticoid steroid with anti-inflammatory activity and toxicological profile typical of its class. Claims in the labeling related to mechanisms of action and precautions related to glucocorticoid activity are appropriate for a drug of this class.

*DRUG ACTIVITY RELATED TO PROPOSED INDICATION:*

***In Vitro* Studies**

**Receptor Binding Assays:** Budesonide is a racemic mixture of two diastereoisomers; both have glucocorticoid activity. The R-isomer has 2-3 times greater glucocorticoid binding affinity than the S-isomer. The glucocorticoid binding affinity of the racemic budesonide mixture is about seven times greater than that of dexamethasone, and about half that of fluticasone propionate. Binding affinity relative to some other glucocorticoids is summarized in table 1, below. Values are geometric means from several studies in human and animal target tissues including thymus and lung. For steroids with a free C21-OH, binding affinity was strongly correlated to lipophilicity (reference 82, Wurthwein et al). As shown in figure 1 below, the topical activity of budesonide and other lipophilic corticosteroids is proportional to their glucocorticoid receptor affinity.

**Table 1. Relative Receptor Affinity of Glucocorticoids**

| Agent | Affinity* | Agent | Affinity* |
|---|---|---|---|
| tipredane | 27.0 | triamcinolone acetonide | 3.1 |
| fluticasone propionate | 15.1 | flunisolide | 1.7 |
| (R) budesonide | 11.2 | dexamethasone | 1.0 |
| beclomethasone monopropionate | 10.2 | prednisone | 0.8 |
| (RS) budesonide | 6.7 | beclomethasone dipropionate | 0.7 |
| (S) budesonide | 4.2 | hydrocortisone (cortisol) | 0.06 |
| methylprednisolone | 4.2 | | |

* Binding affinity relative to dexamethasone = 1; data from references 6, 10, 11, 16, 17, 82.

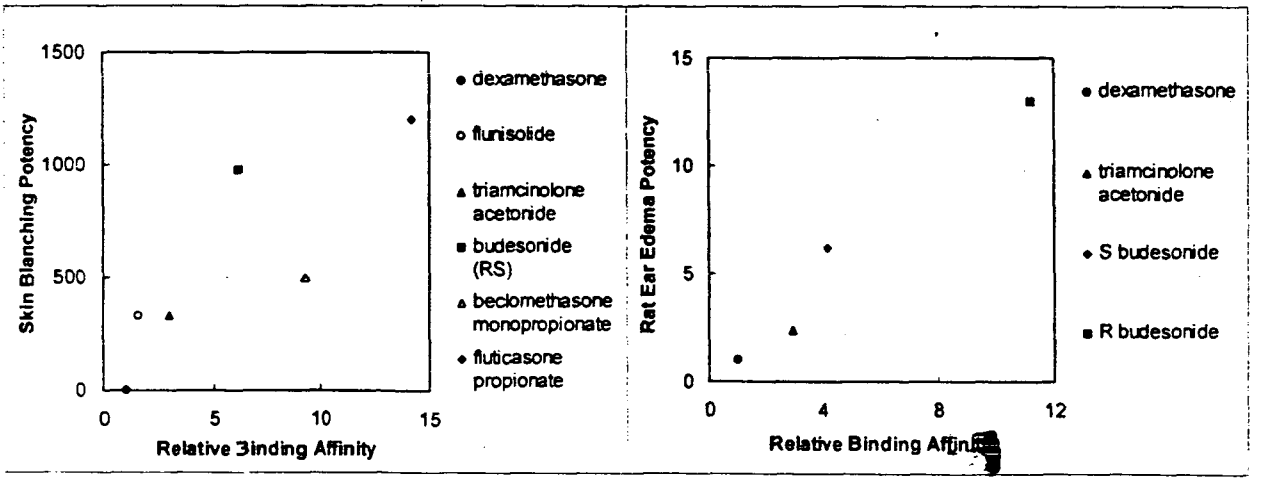



**Figure 1.** Topical potency of corticosteroids in humans (skin blanching) and rats (inhibition of ear edema) in relation to glucocorticoid receptor binding affinity. Binding affinity is relative to dexamethasone = 1; data from references 6, 10, 11, 16, 17.

**Functional Assays:** As expected for a glucocorticoid, budesonide inhibits many inflammatory processes *in vitro*. Any of these might contribute to anti-inflammatory efficacy *in vivo*, but the actual contribution of the different possible mechanisms is unknown. Cytokines mediate a multitude of pro-inflammatory actions. Table 2, below, summarizes studies in which budesonide inhibited cytokine production by blood monocytes, alveolar macrophages, lymphocytes, and respiratory epithelium. Table 3, page 11, summarizes studies in which budesonide altered inflammatory processes in different cell types. Effects on monocytes and lymphocytes include: inhibition of inflammatory cell activation (as measured by surface expression of HLA-DR), increased expression of neutral endopeptidase in epithelium (associated with protection against inflammatory peptides), inhibition of T-lymphocyte mediated monocyte and lymphocyte proliferation, and inhibition of natural killer (NK) cell cytotoxicity. Effects on eosinophils include: decreased survival, inhibition of differentiation from progenitor basophils, inhibition of locomotion and activation (as measured by respiratory burst). Budesonide inhibited expression of adhesion molecules (ICAM-1, E-selectin, VCAM-1) on epithelial or endothelial cells, and inhibited release of eosinophil chemotactic factors by bronchial cells and monocytes. Budesonide decreased cytotoxicity of activated blood monocytes and neutrophils toward fibroblasts, inhibited induction of myofibroblast phenotype in fibroblasts, and inhibited induction of mast cell growth factor in fibroblasts.

**Table 2: Inhibition of Cytokine Formation by Budesonide**

| Cytokine | Cell Type | Trigger | Concentration | Ref. * |
|---|---|---|---|---|
| IL-1 | human PBM | LPS, anti-CD3-Ab | $10^{-9}$ - $10^{-7}$ M | 19 |
| IL-1 | human PBM | allergen | $10^{-9}$ M | 20 |
| IL-2 | human PBM | allergen, anti-CD3-Ab | $10^{-8}$ - $10^{-7}$ M | 19, 20 |
| IL-2 receptor | human PBM | allergen | $10^{-9}$ M | 20 |
| IL-3 | human PBM | allergen | $10^{-8}$ M | 21 |
| IL-4, IL-5 | mouse Th-2 like cell line | anti-CD3-Ab | $10^{-9}$ M | 22 |
| IL-5 | human PBM | allergen | $10^{-8}$ M | 21 |
| IL-6 | human PBM | LPS, anti-CD3-Ab | $10^{-9}$ - $10^{-7}$ M | 19 |
| IL-6 | human AMØ | LPS | $10^{-8}$ M | 19 |
| GM-CSF | human PBM | allergen | $10^{-9}$ M | 20 |
| IFNγ | human PBM | allergen, anti-CD3-Ab | $10^{-8}$ - $10^{-7}$ M | 19, 20 |
| TNFα | human PBM | allergen | $10^{-8}$ M | 20 |
| TNFα | human PBM | LPS, anti-IgG-Ab, quartz, anti-CD3-Ab | $10^{-7}$ M | 19, 23 |
| IL-2, IL-4 | human PBL | anti-CD2 + CD28-Ab | $10^{-8}$ M - $10^{-9}$ M | 24 |
| IL-4, IL-5, IFNγ | mouse Th-2 clone | anti CD3 Ab | $10^{-9}$ M | 24, 25 |
| IL-6, IL-8 | human bronchial epithelial cell line | swine dust, TNFα | $10^{-9}$ M | 26, 27 |
| GM-CSF | nasal epithelial cells | fetal calf serum | max at $10^{-5}$ M | 28, 29 |

Abbreviations: PBM = peripheral blood monocytes; AMØ = alveolar macrophages; PBL = peripheral blood lymphocytes; LPS = lipopolysaccharide; Ab = antibody. *Reference indicates submission numbers listed on pp3-8 of this review.